Environmental Risk Factors for Parkinson's Disease

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Parkinson's disease

- **Chronic, neurodegenerative disorder due to dopamine deficiency**

- **Cardinal features: resting tremor; bradykinesia, gait disturbance, muscle rigidity**

- **First described by James Parkinson, 1817 (thought due to "fright")**

- **Pathological lesion: destruction of dopamine-producing neurons in substantia nigra (Lewy body formation)**

- **Prevalence in US ~150/100,000 (~2% at ages >65)**

- **Incidence in US ~15/100,000**

Figure 8–5. Typical flexed posture of a patient with parkinsonism.

CHEMICAL STRUCTURE OF MPTP. MPP+, AND PARAQUAT

Risk factors for Parkinson's disease

- **Older age: sharp increase over age 50**
- **Male gender: usually slight M:F ratio**
- **Pesticides:**
  - **Paraquat***
  - **Roteneone ***
  - **Organochlorines**
  - **Organophosphates, carbamates, etc.**
- **Metals (Mn, Fe, Cu)**
- **Solvents (??)**
- **Rare genetic mutations (*parkin*, *LRRK2*)**

***Animal models established**

Suspected environmental risk and protective factors for PD

- **Increase risk**
  - **Pesticides**
  - **Metals**
  - **Industrial solvents**
- **Decrease risk**
  - **Cigarette smoke**
  - **Caffeine**
  - **Anti-oxidant micronutrients**
  - **Estrogen**
  - **Anti-inflammatory medications**

PD relative risk by cumulative cigarette smoking history*
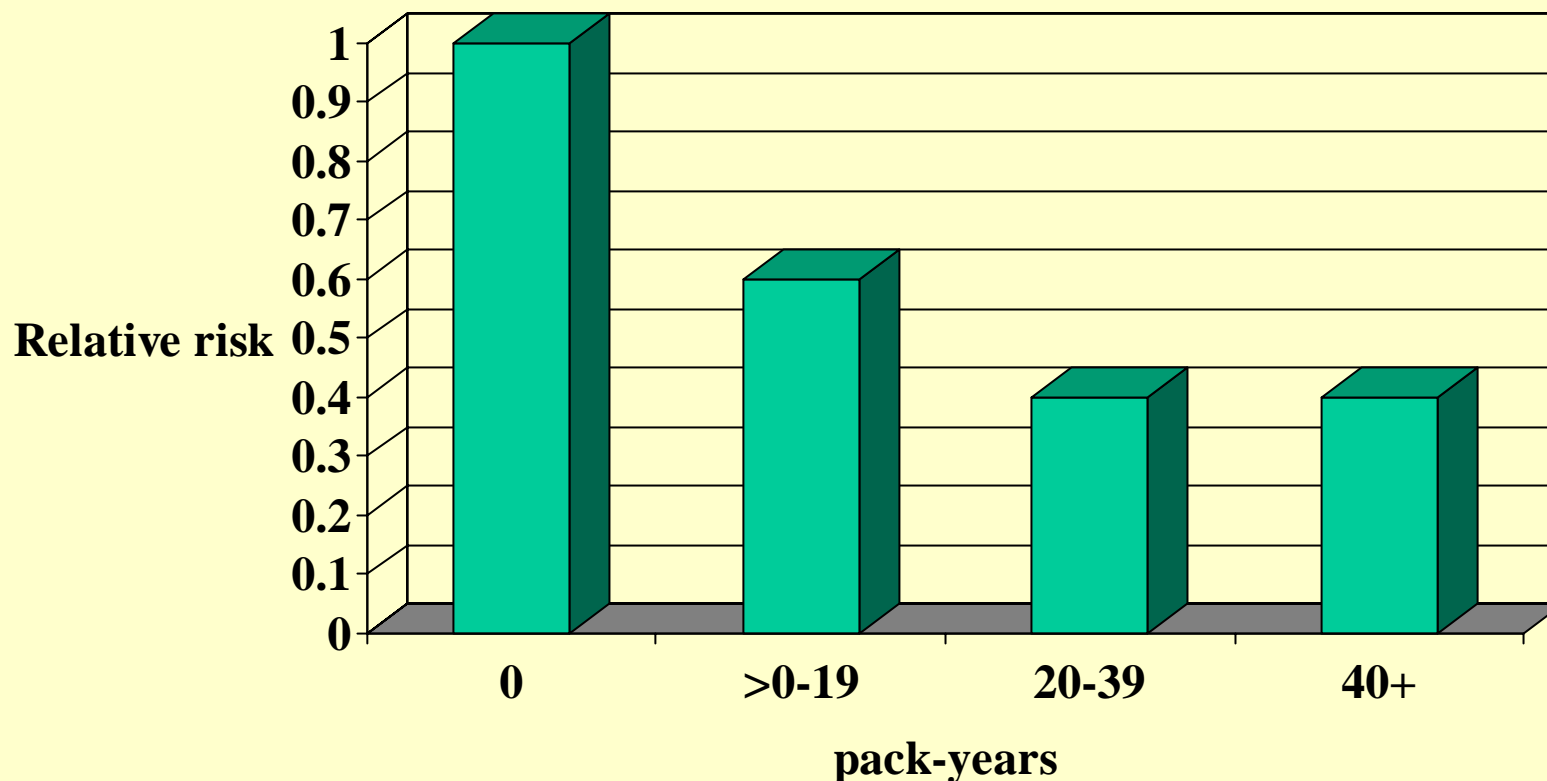
*Checkoway H, et al. *Am J Epidemiol* 2002;155:732-8

Pesticides and Parkinson's disease

- **Many pesticides neurotoxic**
- **Structural similarity of MPTP and paraquat**
- **Animal studies**
  - **Paraquat + Mn interactions on nigral destruction**
  - **Rotenone model of PD induction in mice**
- **Epidemiologic studies**
  - **Ecological correlation studies**
  - **Case-control studies (paraquat, OPs, organochlorines)**
  - **Brain tissue studies (organochlorines)**

Case-control study of pesticides and Parkinson's disease in Germany*

Exposure	Years used	Cases	Controls	OR [+]
Herbicides	0	238	287	1.0
	1-40	59	44	1.7
	41-80	34	15	3.0
	>80	20	10	2.4
Insecticides	0	213	258	1.0
	1-40	70	55	1.8
	41-80	46	25	2.5
	>80	21	14	2.1
Organo-chlorines	Never	262	309	1.0
	Ever	7	2	5.8

[+]Odds ratio, adjusted for age, gender, smoking

*Seidler A, et al. *Neurology* 1996;46:1275-84

Case-control study of pesticides in Taiwan*

Exposure variable	Years used	Cases	Controls	OR[+]
Herbicides/ pesticides	0 1-19 ≥20	74 14 32	199 21 20	1.0 1.5 4.5
Paraquat	0 1-19 ≥20	89 7 24	218 13 9	1.0 1.2 6.4

[+] Odds ratio, adjusted for age, gender, smoking

*Liou HH, et al. *Neurology* 1997;48:1583-8

Pesticide-related occupations worked at least 6 months and PD in men: Seattle study*

Occupation	Cases (N=135)	Controls (N=226)	OR[+]
Dairy farmer	14	28	0.81
Orchardist	6	9	1.49
Pesticide applicator	4	4	3.88
Farmer – any	45	69	1.25

[+]Odds ratio, adjusted for age, smoking

*Firestone J, et. *Arch Neurol* 2005;62:91-5

Self-reported pesticide occupational pesticide exposures and PD, men: Seattle study*

Exposure	Duration (yrs)	Cases (N=135)	Controls (N=226)	OR[+]
Any pesticide	0.5-5	6	10	1.0
	>5	10	12	1.3
Insecticides	0.5-5	5	11	0.9
	>5	9	11	1.2
Herbicides	≥0.5	2	6	0.6
Paraquat	0.5-5	0	1	0
	>5	2	1	3.2

[+]Odds ratio, adjusted for age, smoking

*Firestone J, et. *Arch Neurol* 2005;62:91-5.

Parkinson's disease risk in an elderly French cohort, 1992-98*

Exposure	Men		Women	
	RR[+]	95% CI	RR[+]	95% CI
Occupational	5.6	1.5-22	1.0	0.2-4.8
Main job in agriculture	1.6	0.3-8.6	0.8	0.1-6.4
Rural residence	1.5	0.4-5.5	1.3	0.4-4.3
Residence in vineyard district	0.5	0.1-2.3	0.9	0.2-3.2

Relative risk, adjusted for smoking, education

*Baldi I et al. (2003) *Am J Epidemiol* 157:409-14

Prospective cohort study of PD in men and years worked on Hawaiian plantations: 1965-96*
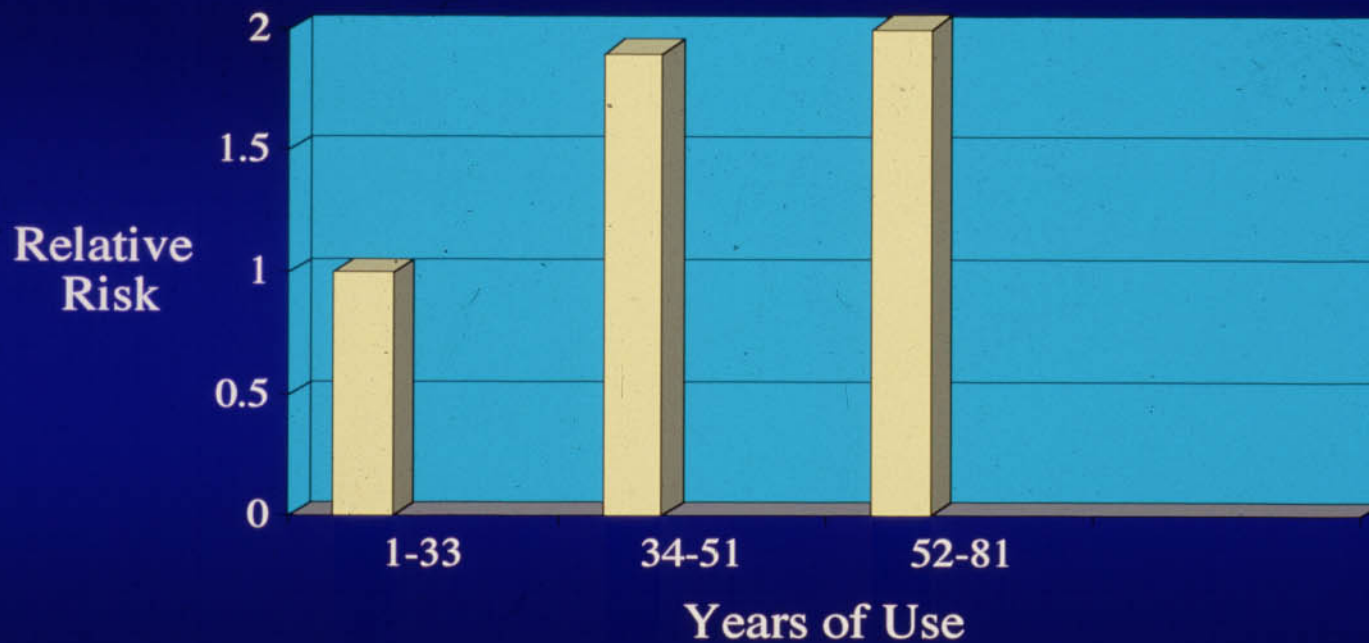
Duration (yrs)	No. subjects	Cases	RR[++]	95% CI
0	5363	73	1.0	Ref
1-10	1843	24	1.0	0.6-1.6
11-20	315	7	1.7	0.8-3.7
>20	465	12	1.9	1.0-3.5

[*]Petrovitch H, et al. *Arch Neurol* 2002;59:1787-92
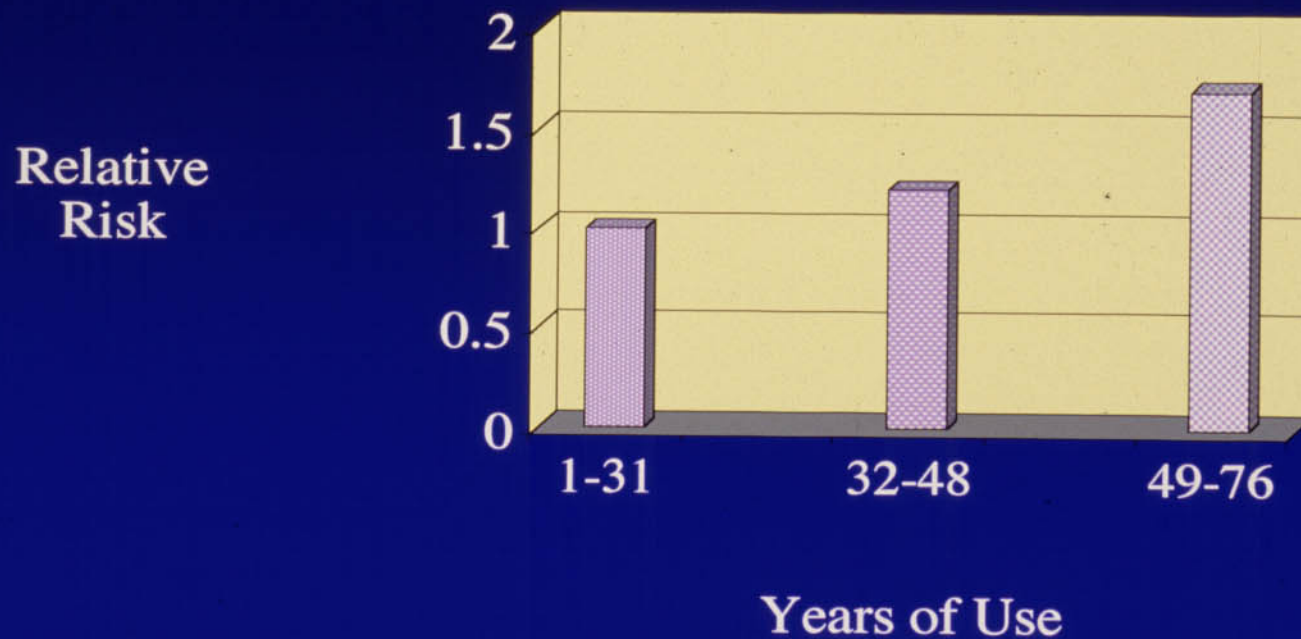
[+]Sugarcane or pineapple

[++]Relative risk adjusted for age, pack-yrs smoking, coffee consumption

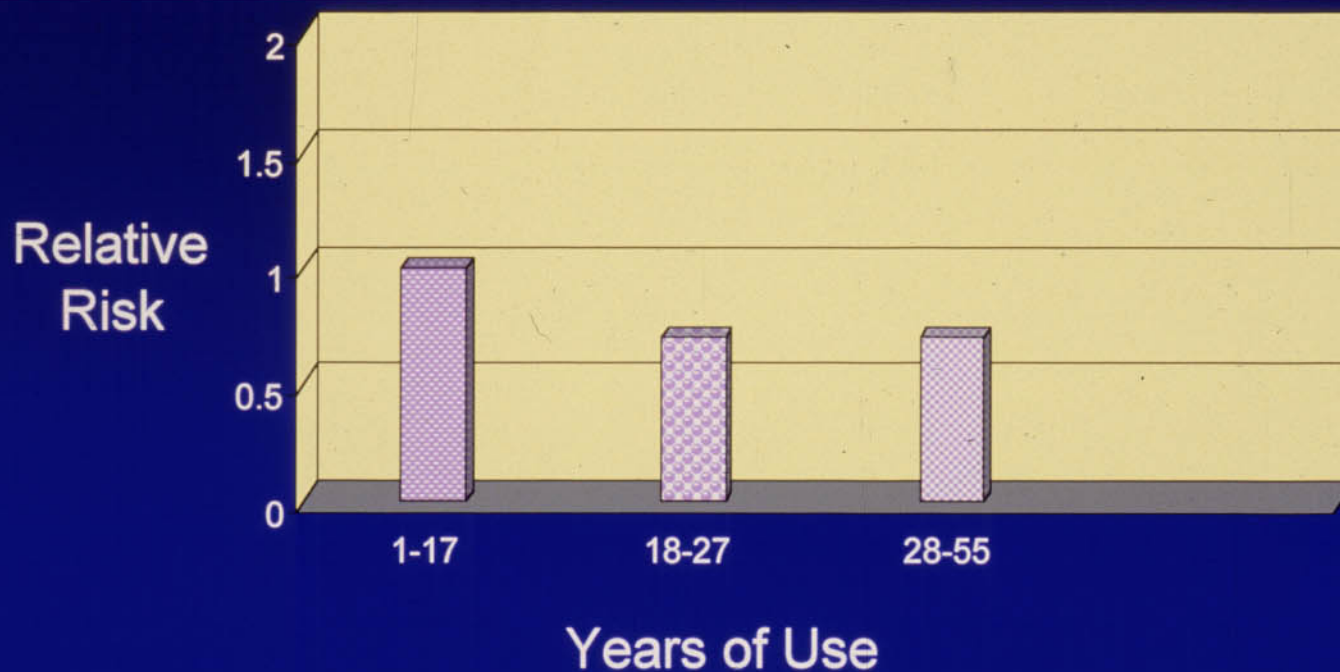Pesticide Exposures and Parkinsonism: Any Pesticides

Engel L, et al. *Occup Environ Med* 2001;58:582-9

Insecticide Exposures and Parkinsonism

Engel L, et al. *Occup Environ Med* 2001;58:582-9

Herbicides Exposures and Parkinsonism

Engel L, et al. *Occup Environ Med* 2001;58:582-9

Evidence for metals as PD risk factors

- **Chronic manganism similar clinical features as PD**

- **Mn, Fe involved in free radical formation (via Fenton reaction)**

- **Elevated concentrations of various metals in PD brain (mixed evidence)**

Occupational metal exposures and PD:
Detroit area case-control study*

Metal	Exposure (yr)	Relative risk	95% CI
Lead	≤20	1.08	0.55-2.13
	>20	2.05	0.97-4.31
Iron	≤20	1.02	0.59-1.75
	>20	1.27	0.69-2.34
Copper	≤20	1.15	0.55-2.41
	>20	2.49	1.06-5.89
Manganese	≤20	0.40	0.05-3.24
	>20	10.6	1.06-106

*Gorell JM et al. (1997) *Neurology* 48:650-8

Combined occupational metal exposures and PD: Detroit area case-control study*

Metals	Exposures	Relative risk	95% CI
Lead + Copper	Both >20 yr	5.25	1.59-17.2
Lead + Iron	Both >20 yr	2.84	1.07-7.50
Iron + Copper	Both >20 yr	3.69	1.40-9.71

*Gorell JM et al. (1997) *Neurology* 48:650-8

Parkinsonism prevalence among Alabama welders and boilermakers compared to general population rates*

Occupational group	*Prevalence ratio+*	*95% CI*
Boilermakers	10.3	2.6-40.5
Welders	7.3	3.1-17.1
Welder helpers	9.0	2.8-29.1
Combined	7.6	3.3-17.7

*Racette B, et al. (2005) *Neurology* 64:230-5

+Compared to prevalence in Copiah County, MS

Challenges in identifying environmental risk factors for PD

- **Case ascertainment—diagnostic uncertainty, few pop. based registries**

- **Difficulties of accurate exposure assessment**

- **Probably low attributable risks for specific agents**

- **PD is a complex disease—potentially multiple phenotypes**

Recommendations for future research

- **Better characterization of genetically-determined susceptibility factors (gene/environment interactions)**

- **Increased focus on populations with well documented exposures (e.g., pesticide applicators, welders, cotton textile workers exposed to endotoxin)**

Sometimes break-throughs occur!